locations occupied by the cells, thereby generating, for each individual cell measured, a set of data; generating a histogram showing the distribution of the mass tags across the test population of cells; and comparing the histogram to a reference histogram obtained from a reference population of cells.

[0015] In any of these embodiments, the method may further include identifying one or more cells of interest based on a threshold value for the abundance of the one or more mass tags. In some cases the threshold value is determined based on the reference histogram.

[0016] In any of these embodiments, the test population of cells may have been contacted with a test agent and the reference population of cells has not been contacted with the test agent.

[0017] In any of these embodiments, the test population of cells may be obtained from a subject diagnosed with a condition and the reference population of cells is obtained from a healthy subject.

[0018] Also provided herein is an automated system for analyzing an array of cells. In certain embodiments, the system may include a SIMS system comprising a holder for retaining a substrate comprising an array of cells, wherein the cells are labeled with one or more mass tags and are separated from one another, wherein the system is configured to (i) measure the abundance of the one or more mass tags at a plurality of locations occupied by the cells of the array using SIMS, (ii) generate a data set that comprises the measurements of the abundance of the one or more mass tags, and (iii) output the data set, and a computer comprising an analysis module that analyzes the data set.

BRIEF DESCRIPTION OF THE FIGURES

[0019] The skilled artisan will understand that the drawings, described below, are for illustration purposes only. The drawings are not intended to limit the scope of the present teachings in any way.

[0020] FIG. **1** shows schematic representations of a random (left) and addressable (right) array of cells on a substrate, according to embodiments of the present disclosure.

[0021] FIG. **2** shows schematic representations of primary ion beam diameters relative to a cell, according to embodiments of the present disclosure.

[0022] FIG. **3** shows a schematic representation of single cell mass tomography using SIMS analysis, according to an embodiment of the present disclosure.

[0023] FIG. **4** shows a depth profile of the abundance of mass tags configured to label different subcellular structures in a T-cell, according to an embodiment of the present disclosure.

[0024] FIG. **5** shows subcellular colocalization of different mass-tag labels, according to an embodiment of the present disclosure.

DEFINITIONS

[0025] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present teachings, some exemplary methods and materials are now described.

[0026] "Binding," as used herein, refers to a specific interaction between any two members, e.g., two proteins, two nucleic acids, a protein and a nucleic acid, etc., where the affinity between a two specific binding members is characterized by a K_D (dissociation constant) of 10^{-5} M or less, 10^{-6} M or less, such as 10^{-7} M or less, including 10^{-8} M or less, e.g., 10^{-9} M or less, 10^{-10} M or less, 10^{-11} M or less, 10^{-12} M or less, 10^{-13} M or less, 10^{-14} M or less, 10^{-15} M or less, including 10^{-16} M or less. "Affinity" refers to the strength of binding, increased binding affinity being correlated with a lower K_D.

[0027] The term "specific binding" refers to the ability of a binding reagent to preferentially bind to a particular analyte that is present in a homogeneous mixture of different analytes. In certain embodiments, a specific binding interaction will discriminate between desirable and undesirable analytes in a sample, in some embodiments more than about 10 to 100-fold or more (e.g., more than about 1000- or 10,000-fold).

[0028] As used herein, the term "specific binding reagent" refers to a labeled reagent that can specifically bind to one or more sites in a specific molecular target (e.g., a specific protein, phospholipid, DNA molecule, or RNA molecule) in or on a cell. Specific binding reagents include antibodies, nucleic acids, and aptamers, for example. A used herein, an "aptamer" is a synthetic oligonucleotide or peptide molecule that specifically binds to a specific target molecule.

[0029] By "antibody" is meant a protein of one or more polypeptides that specifically binds an antigen and that are substantially encoded by all or part of the recognized immunoglobulin genes. The recognized immunoglobulin genes, for example in humans, include the kappa (κ), lambda (λ), and heavy chain genetic loci, which together contain the myriad variable region genes, and the constant region genes mu (μ), delta (δ), gamma (γ), sigma (σ), and alpha (α) which encode the IgM, IgD, IgG, IgE, and IgA antibody "isotypes" or "classes" respectively. Antibody herein is meant to include full length antibodies and antibody fragments, and may refer to a natural antibody from any organism, an engineered antibody, or an antibody generated recombinantly for experimental, therapeutic, or other purposes. The term "antibody" includes full length antibodies, and antibody fragments, as are known in the art, such as Fab, Fab', F(ab')2, Fv, scFv, or other antigen-binding subsequences of antibodies, either produced by the modification of whole antibodies or those synthesized de novo using recombinant DNA technologies. Methods for generating antibodies that bind specifically to a target protein or antigen of interest are known. See, e.g., Greenfield, infra.

[0030] The terms "polynucleotide", "nucleotide", "nucleotide sequence", "nucleic acid", "nucleic acid molecule", "nucleic acid sequence" and "oligonucleotide" are used interchangeably, and can also include plurals of each respectively depending on the context in which the terms are utilized. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides (DNA) or ribonucleotides (RNA), or analogs thereof. Polynucleotides may have any three-dimensional structure, and may perform any function. The following are non-limiting examples of polynucleotides: coding or non-coding regions of a gene or gene fragment, loci (locus) defined from linkage analysis, exons, introns, messenger RNA (mRNA), transfer RNA (tRNA), ribosomal RNA, ribozymes, small interfering RNA, (siRNA), microRNA (miRNA), small nuclear RNA